PATENT
Customer No. 22,852
Attorney Docket No. 07580.0008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Satoshi YOSHIDA *et al.*	)	Group Art Unit: 1655
	)	
Application No.: 10/553,798	)	Examiner: C. Chen
	)	
Filed: October 18, 2005	)	
	)	
For: AGENT FOR INCREASING GRANULOCYTE MACROPHAGE COLONY STIMULATING FACTOR	)	Confirmation No.: 6122

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

In reply to the final Office Action mailed January 15, 2010, Applicants respectfully request panel review of the twice rejected claims. A Notice of Appeal was previously filed on October 15, 2007, and a request to reinstate that appeal accompanies this Request. This reply is due April 15, 2010, and is timely filed.

No amendments are being filed with this Request. Applicants' remarks begin on page 2.

REMARKS

Claim 2 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over JP 2000-281584 to Yamanouchi Pharmaceuticals ("Yamanouchi") in view of Levine *et al.*, Int Conf AIDS (1989) 5:406 ("Levine") Nissen *et al.*, Blood (1998) 72:2045-72 ("Nissen") and Weisbart *et al.*, Nature (1985) 314:361-63 ("Weisbart"). Office Action, page 3. Claim 3 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Yamanouchi in view of Kojima *et al.*, Blood (1991) 77:937-41 ("Kojima") and Falanga *et al.*, Blood (1999) 93:2506-14 ("Falanga"). Office Action, page 4.

Applicants respectfully traverse each of these rejections at least because the combination of references does not provide a technical basis from which the ordinary artisan could have reasonably expected that the composition recited in the claims could be used to treat neutropenia (claim 2), or aplastic anemia (claim 3). Applicants' have previously discussed in detail in their October 28, 2009, response why the rejections fail to meet the requirements for establishing a *prima facie* case of obviousness. This Requests incorporates those reasons by reference and focuses on the technical reasons that the references do not support the Office's position.

The Office's obviousness argument hinges on its assumption that there is a reasonable expectation that a neutrophil ***activator*** can be used to treat neutropenia or aplastic anemia. Rosenberg & Gallin (of record) provide an overview on pages 1056-1058 of the steps that lead to the development of the ability of neutrophils to mediate an inflammatory response, *i.e.*, to become "activated" neutrophils. Different drugs affect different, and sometimes multiple, aspects of neutrophil biology. As summarized in Table 1 of Rosenberg (p. 1058), both GM-CSF and G-CSF contribute to the process of

neutrophil maturation so that the cells can be released into the circulation. In Table 1 this activity is described as "stimulates maturation within the bone marrow." In addition, both GM-CSF and G-CSF also have roles in neutrophil priming, which is necessary to obtain an activated neutrophil. Thus, GM-CSF and G-CSF were known to each act at two *distinct* steps in the multi-step process that leads to the development of activated neutrophils. But not all drugs affect both neutrophil release and activation. For example, IL-8 does not alter neutrophil release from the bone marrow; instead it acts to promote chemotaxis (movement to the site of inflammation) and to induce degranulation and NADPH oxidase activity, which are effector functions of activated neutrophils. Thus, knowing a drug can mediate neutrophil activation says nothing about its ability to stimulate neutrophil release into the circulation. In fact, neutrophil-activating drugs sometimes cause the rapid *clearance* of neutrophils from the circulation, *resulting in neutropenia*, if the body is not able to release new neutrophils from the bone marrow. This is why neonates, who have limited capacity to release neutrophils from the bone marrow, may develop neutropenia in response to sepsis (which involves neutrophil activation). *See, e.g.*, Gillian et al., Blood 1994; 84:1427-33 and Cairo et al., Blood 1995; 86:2509-15. Treating the neonates with G-CSF or GM-CSF helps correct the neutropenia by promoting neutrophil maturation and release from the bone marrow. Gillian, p. 1431; Cairo, p. 2514.

In each rejection, Yamanouchi is the primary reference. The Office relies upon it for its teaching that the claimed crude drug ***activates*** neutrophils. Office Action at 2, 4, 5, 6. The secondary references cited in the rejection of claim 2 show that 1) GM-CSF is a neutrophil activating factor (Weisbart) and that 2) GM-CSF can be used to treat

neutropenia (Levine). The secondary references relied upon in the rejection of claim 3 show that 1) G-CSF is a neutrophil activating factor (Falanga) and that 2) G-CSF can be used to increase the neutrophil count to treat aplastic anemia (Kojima). The Office alleges from these teaching it would have been obvious to use the neutrophil-activating crude drug of Yamanouchi in methods of treating neutropenia and aplastic anemia.

However, for the Office's rationale to apply, GM-CSF must treat neutropenia and G-CSF treat aplastic anemia because those growth factors *activate* neutrophils. That assumption is inconsistent with the references' teachings. First, as discussed in detail in the 10/28/09 response, the secondary references teach that it is the ability of GM-CSF and G-CSF to promote *proliferation and differentiation* of neutrophil progenitors so that the number of circulating neutrophils increases that provides the basis for using them in treating neutropenia and aplastic anemia. Nissen, p. 2047; Falanga, p. 2056; Kojima, Abstract. Second, Rosenberg Table 1 shows that *not all neutrophil activators also stimulate release from the bone marrow*. GM-CSF and G-CSF have both activities, but IL-8, LTB4, fMLP, and most other activators do not. Thus, knowing that Yamanouchi's crude drug is a neutrophil activator *does not provide a basis for predicting that it can either directly or indirectly increase neutrophil numbers to treat neutropenia or aplastic anemia, as claimed*. Indeed, as noted *supra*, neutrophil activation was known in the art to sometimes *contribute* to neutropenia.

It is only Applicant's disclosure that shows that the claimed composition has the ability to increase GM-CSF production *in vivo*. And it is only once the ordinary artisan understands that the claimed composition can increase levels of GM-CSF that there becomes a reasonable expectation that the composition could be used to treat

conditions in which maturation and release of neutrophils is impaired. The Office has not pointed to anything in Yamanouchi that would provide a reasonable basis for predicting that the crude drug would increase GM-CSF activity or otherwise have any effect on neutrophil maturation and release from the bone marrow. Instead, Yamanouchi shows only that the crude drug increases functions associated with neutrophil activation. Yamanouchi, paragraphs 0017-0022.

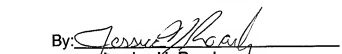
Applicants respectfully submit that the references cited by the Office do not provide a reasonable expectation of success because function as a neutrophil activator does not provide a basis for using a drug to treat neutropenia or aplastic anemia. Applicants therefore respectfully request that the Office withdraw the rejections and pass the claims to issue.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 8, 2010

By: 
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